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Dr. James F. Couch of the Eastern Regional Research Laboratory, where much of the Research on Rutin has been done.

(See p. 164 for article on Rutin.)

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CONTENTS

PAGE

Editorial:

How Many Students? 154

Articles:

Phytochemical Study of Nereocystis Luetkeana. By R. W. Sager, L. Arrigoni and L. Fischer 156

Rutin and Capillary Fragility. By E. Johnson 164

Organizing a Mule. By T. Swann Harding 176

Selected Abstracts 183

Solid Extracts 187

E D I T O R I A L

HOW MANY STUDENTS?

WITHIN a period of less than two years one of the most pressing problems confronting our colleges has been completely reversed. Two years ago colleges, trying to supplement their dwindling enrollment, were urging by all sorts of inducements the few young men available and women to enter upon the study of pharmacy. Their motives were not purely selfish for indeed the clamor for trained pharmacists was both loud and incessant and many having the true interests of pharmacy at heart looked with chagrin while standards for licensure were lowered here and there as a result of the pressure exerted by those unwilling to forego the convenience of a ready supply of low-salaried personnel.

Today, how different is the problem confronting college administrators! Most colleges have from five to ten times the number of applicants that can be accommodated using the very maximum of their facilities, and the end is not yet in sight. Those who might have enrolled over the past five years but for the war constitute a large enough group to cause serious trouble, but this number is greatly multiplied by many who would be unable to afford a college training but for the so-called GI Bill with its educational benefits. The fully-warranted publicity and glamor given to "life-saving drugs" on the battlefield has also motivated toward pharmacy many corpsmen and pharmacist mates who might otherwise not have considered it as a career. The net result is almost chaos and college deans themselves are not sure of what should be done.

Some facts concerning the problem seem fairly certain. There is undoubtedly a great demand for pharmacists, both because of the paucity of graduates during the last five years and the increased opportunities afforded pharmacists due to improved drug standards requiring skilled workers and representatives. This demand can in time not only be saturated but an oversupply of pharmacists is inevitable with all its attendant evils unless some limitation of enrollment is adopted as a matter of policy by our colleges. The colleges this year might take the maximum number of students that is compatible with good

instruction based on their existing faculties and equipment, but to greatly expand their facilities and continue this policy is to invite disaster to the profession. The expansion of physical facilities—lecture rooms, laboratories and apparatus still does not provide good teachers and these are not rapidly produced. Even with the best of equipment and teaching the dangers of turning out thousands of pharmacists must be obvious to those who recall that orgy of overproduction which we witnessed in the twenties with pharmacists pushed lower and lower in the economic picture until they even yet have not fully recovered from that sense of inferiority for which the colleges are really responsible.

The burning question today is—are the colleges and is pharmaceutical education sufficiently mature to meet this challenge in such a way as to protect pharmacy and pharmacists from hordes of would be pharmacists far exceeding the potential demand? This question must be answered and with a solid front. The delegates attending the meeting of the American Association of Colleges of Pharmacy in August will find this question high on its agenda. They should face this problem courageously and with immediate benefits and self-interest subjugated to the common good and welfare of pharmacy.

L. F. TICE.

A PHYTOCHEMICAL STUDY OF NEREOCYSTIS LUETKEANA

By Robert W. Sager,* Louis Arrigoni ** and Louis Fischer ***

THE abundance of *Nereocystis luetkeana,* or Bladder Kelp, in the vicinity of Puget Sound, coupled with the many and varied uses of certain of its constituents led to the present study.

The investigation was divided into three parts—first, an analysis of the ash, which constitutes approximately one-half the dry weight of the plant. Little work on this phase of the subject has been published for nearly thirty years, and many of the analyses then reported were performed on either the effloresced salts or water lixiviates. It seemed reasonable to assume that an analysis of the total ash would be more representative, since both the effloresced salts and water lixiviates could conceivably vary under different conditions and methods of preparation.

Second, in view of the wide usage of alginic acid, a quantitative estimation of this constituent was undertaken.

Third, attempts were made to detect the presence of laminarin, a storage carbohydrate common to related brown algae, as no reports of this constituent in *Nereocystis luetkeana* were found in the literature.

Experimental

The samples used in the analysis were collected and identified by Dr. George B. Rigg at the Oceanographic Laboratories of the University of Washington at Friday Harbor on August 12, 1938. The stipes and fronds were individually air-dried, ground and stored in

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air-tight glass jars and analyzed separately. Standard chemical procedures applying to this type of analysis were followed. All results of the analyses are based on the dry weight of the plant.

Proximate Analysis

TABLE I

	Stipes Per Cent	Fronds Per Cent
Crude Fiber	6.70	5.89
Organic and Ammoniacal Nitrogen	1.10	1.97
Starch	Absent	Absent
Reducing Sugars	Absent	Absent
Total Ash	59.29	47.29
Water-Soluble Ash	55.49	42.65
Water-Insoluble Ash	3.80	4.64
Acid-Insoluble Ash	0.08	0.09

Composition of the Ash

TABLE II

	Stipes Per Cent	Fronds Per Cent
Sulfates as SO_4	1.77	6.28
Phosphates as P_2O_5	1.11	2.91
Iodine	0.08	0.16
Chlorine	46.90	38.59
Bromine	Trace	Trace
Calcium Oxide	2.25	3.09
Magnesium Oxide	3.43	3.17
Potassium	27.85	31.43
Sodium	15.12	11.17

Alginic Acid

Twenty-five gram samples of the air-dried, ground plant were suspended in a two per cent solution of sodium carbonate, which reacts with alginic acid to form soluble sodium alginate. The mix-

ture was shaken at one hour intervals for four hours, then allowed to stand overnight. The supernatant liquid was siphoned off and filtered with suction. This procedure was repeated until complete extraction of the alginic acid had been obtained.

The combined solutions of sodium alginate were then acidified with an excess of dilute hydrochloric acid, thus precipitating free alginic acid, which separated out in light colored flocculent masses suspended throughout the solution. The precipitate was then filtered off with suction and washed with cold water until free from hydrochloric acid.

After thorough washing with water, the alginic acid was redissolved in 2 per cent sodium carbonate solution, filtered with suction to remove any extraneous material still present, reprecipitated with dilute hydrochloric acid, filtered and washed free from hydrochloric acid. This procedure was repeated for a third time to insure complete purification.

After the third hydrochloric acid precipitation, the alginic acid was redissolved in 2 per cent sodium carbonate solution and the sodium alginate separated by the addition of 95 per cent alcohol. The sodium alginate was filtered with suction, then dissolved in water. Free alginic acid was reprecipitated with dilute hydrochloric acid, filtered, washed with cold water until the hydrochloric acid was removed and dried to constant weight.

	Stipes	Fronds
Alginic Acid, per cent	15.33	20.96

Laminarin

The procedure of Barry (1) was followed in the first attempt to isolate and identify laminarin in *Nereocystis luetkeana*. Separate 100 gram samples of stipes and fronds of the air-dried plant were covered with 5 per cent hydrochloric acid, shaken well and allowed to macerate four days, with thorough shaking once each day. At the end of the fourth day, the mixture was again shaken, allowed to settle, and the supernatant liquid decanted off. This procedure was repeated four times in order to insure complete extraction of any laminarin that might be present.

The combined acid extracts were then strained through coarse muslin, the residue and muslin washed with 5 per cent hydrochloric

acid, and the filtrate set aside several days to allow spontaneous deposition. A small amount of finely divided material was observed to settle out, while the supernatant liquid remained turbid. The mixture was then centrifuged, allowed to stand one day, the clear supernatant liquid siphoned off, and this procedure repeated until all of the suspended material had been centrifuged out. Hot water was then added to the residue, the mixture set aside overnight, centrifuged and the water removed with suction. This process was repeated six times with hot water, then 95 per cent alcohol was substituted for the hot water and the mixture shaken, allowed to stand overnight, centrifuged and the alcohol siphoned off. This procedure also was repeated six times.

The residue was a light brown amorphous mass and its physical appearance did not conform to the descriptions of the carbohydrate, laminarin, as reported in the literature. In an attempt to hydrolyze this material it was heated in an autoclave at 120° C. (15 pounds pressure) for 4 hours in 12 per cent hydrochloric acid. Following hydrolysis, a dark residue remained in the mixture indicating that very little or none of the previously described material was dissolved by the hydrolytic procedure. Since any glucose produced would be in solution, the precipitate was filtered off and portions of the resulting filtrate were neutralized and heated with Fehling's solution, but no reduction could be detected. Several attempts were made to prepare osazones with this same solution, but none was successful. It was concluded that the substance extracted from *Nereocystis luetkeana* by this method was not similar to the laminarin reported in *Laminaria digitata* and other species of the brown algae.

With the thought in mind that laminarin might be present in *Nereocystis luetkeana* in minute quantities, a one kilogram composite sample, consisting of the air-dried fronds of five different collections between June and December, 1938, was macerated with hot water overnight and the supernatant liquid decanted off. This procedure was repeated four times, after which the combined extracts were filtered through cheesecloth to remove any extraneous material carried over during decantation. Since some of the algin is also dissolved out of the plant with hot water, dilute hydrochloric acid was added and the precipitated alginic acid filtered off through muslin. The mixture was allowed to stand 2 days, during which time a light precipitate settled out. The supernatant liquid was then siphoned

off, the residue washed repeatedly by decantation with successive portions of hot water and the precipitate allowed to settle out in the intervals between washings. The purification procedure was continued, using 95 per cent alcohol, until no further color change in the light brown, flocculent precipitate could be observed.

The material thus obtained was suspended in 12 per cent hydrochloric acid, heated in an autoclave at 120° C. for 2½ hours, then tested for reducing substances with Fehling's solution and with phenylhydrazine for the formation of osazones. No reduction was observed and no osazones were obtained. It was concluded that the material extracted by this method was not laminarin, since the laminarin from *Laminaria digitata* and other species of *Laminaria* reported in the literature is hydrolyzed to glucose, which is reduced by Fehling's solution, and is capable of forming osazones with phenylhydrazine.

Williams (2), in an unpublished work on the laminarin content of *Nereocystis luetkeana,* reported percentages varying from approximately one-half to 2 per cent of a substance causing reduction of a picric acid solution after hydrolysis, which he assumed to be laminarin. No attempt to identify the reducing substance by the preparation of osazones or other means was reported. The procedure followed in this work was, briefly, as follows: 5 gram samples of the air-dried, ground plant were treated with 40 cc. of 85 per cent alcohol, boiled for about one minute in a water bath, then cooled and centrifuged. The supernatant alcohol was decanted off and the extraction repeated with another 40 cc. of 85 per cent alcohol. The alcohol-insoluble residue was then extracted three times with one per cent hydrochloric acid, twice for 6 hours with 40 cc. and again for one hour with 20 cc. The acid extracts were centrifuged, decanted, combined and diluted to 100 cc.

Ten cc. of the acid extract were then heated in an autoclave at 120° C. for two hours. The Benedict-Lewis picric acid method for the determination of reducing sugars was then applied to one cc. portions of the hydrolyzed extract in order to determine the amount of glucose present.

Williams considered the three extractions with one per cent hydrochloric acid sufficient to remove all the laminarin present, and these acid extractions in conjunction with the centrifuging were assumed to have left all the alginic acid in the acid-insoluble residue.

In an attempt to duplicate the results of Williams, extractions following his procedure exactly were performed on separate 5 gram samples of the air-dried stipes and fronds. The extracts, hydrolyzed as directed in his method, were then neutralized and heated with Fehling's solution, and reduction of the same order of magnitude in the stipes and fronds was observed. Other portions of the same hydrolyzed extracts were boiled with phenylhydrazine, but no osazones were formed. Positive Molisch reactions, performed on these same acid extracts, both before and after hydrolysis, established the identity of the substance causing the reduction of the Fehling's solution as a carbohydrate.

This same extraction procedure was repeated, using 10 gram samples of the plant, and the combined acid extracts were neutralized, then evaporated down to 10 cc. on a steam bath. This procedure was performed in an attempt to concentrate all the reducing substances from the 10 gram sample into a small volume which, after hydrolysis according to Williams' method, would concentrate any glucose formed and increase the possibility of forming osazones with phenylhydrazine. No osazones were obtained, however, by the action of phenylhydrazine on this solution.

It was noted that the supernatant liquid from the hot water extraction of the one kilogram sample, previously outlined, had remained turbid after the separation of the precipitate. With the idea in mind that this supernatant liquid had possibly retained laminarin in suspension, 200 cc. of the liquid were concentrated on a steam bath to approximately 25 cc., heated in an autoclave at 120° C. for 2½ hours, and the resultant hydrolyzed mixture tested with Fehling's solution. Moderate reduction was observed, but upon treatment with phenylhydrazine, no osazones were formed. The reduction of Fehling's solution immediately started speculation as to the identity of the reducing substance, and experiments were undertaken to justify reduction of Fehling's solution with the hydrolyzed extract under the supposition that laminarin was absent.

It was felt that even though alginic acid is precipitated by dilute hydrochloric acid and is reported to be insoluble in acid solution, some small portion may have remained in the acid extract since it is a moderately strong acid itself, and caused the reduction of the Fehling's solution. In order to establish the ability of hydrolyzed alginic acid to reduce Fehling's solution, a small amount was thor-

oughly washed with cold water, treated with dilute hydrochloric acid and heated in an autoclave at 120° C. for 2½ hours. The hydrolyzed alginic acid was then tested for reduction with Fehling's solution, and was observed to yield substantial reduction.

Another sample of pure, washed alginic acid was then extracted by Williams' procedure for the recovery of laminarin in an attempt to determine whether some alginic acid may possibly have been extracted by this method. After the acid extraction, the mixture was allowed to settle, decanted off through a filter, and tested for the presence of carbohydrate with Molisch reagent. A good Molisch reaction was obtained which seemed to indicate that the alginic acid was not completely insoluble in one per cent hydrochloric acid and that enough was dissolved to give tests for reducing sugars following hydrolysis. This reduction could very easily be misconstrued to indicate the presence of laminarin in the acid water extractions.

The fact that in the present work reduction was obtained with an acid extract of alginic acid which was comparable to the reduction obtained by a similar acid extract of the air-dried plant, and that no osazones were obtained from the concentrated acid extracts of the plant, would make it appear that the reduction was due to some substance other than laminarin. The above experiments with alginic acid seem to indicate that the reduction of Fehling's solution was due to the presence of small quantities of this material in solution. Furthermore, since the Williams acid extracts were diluted to 100 cc. and only one cc. aliquots taken for analysis, it is logical that even a minute positive error due to alginic acid reduction of the picric acid reagent could, when multiplied by 100 in the calculation back to the original volume, magnify the total error to completely misleading final results.

In view of the fact that numerous and varied attempts were made in the present work to isolate and identify laminarin from *Nereocystis luetkeana,* and since the only effort thus far reported concerning the laminarin content of this sea-weed is considered to be incomplete and the method of extraction inadequate, it is concluded that the carbohydrate laminarin, as found in *Laminaria digitata* and other species of *Laminaria,* is, by methods of extraction and identification used in this work, either entirely absent in *Nereocystis luetkeana* or present in undetectable amounts.

Summary

Separate quantitative analyses of the stipes and fronds of *Nereocystis luetkeana* were performed.

Percentages of ash, crude fiber and nitrogen were reported. Qualitative tests showed the absence of reducing sugars and starch.

The total ash was analyzed for sulfates, phosphates, halogens, calcium oxide, magnesium oxide, potassium and sodium.

Alginic acid was extracted and found to be present in quantities comparable to other species of the brown algae reported in the literature.

The storage carbohydrate laminarin was not found in *Nereocystis luetkeana* by methods used in its extraction from other brown algae as evidenced by the inability to prepare glucosazones from the hydrolyzed acidulated water extractions.

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RUTIN AND CAPILLARY FRAGILITY

By Elof F. Johnson, M. Sc.*

RUTIN, a flavonol glucoside, has recently been found effective in the treatment of increased capillary fragility, a condition in which the walls of the capillaries are abnormally fragile. The cause of this fragility is not thoroughly understood by the medical profession.

A brief review of the general structure and physiology of the circulatory system will be considered to show the importance of the capillaries in normal metabolism. The blood vessels of the body form a continuous closed system made up of three main divisions: (1) the arterial system carries blood away from the heart; (2) the venous system collects and returns the blood to the heart; (3) the capillaries form a vast network of minute vessels which pervade every tissue of the body and serve to join the arterial and venous system. It is in the capillaries that the exchange of oxygen and food occurs, to be replaced with the carbon dioxide and other waste products of the cells.

The wall of a capillary consists of a fine transparent endothelial layer composed of cells joined edge to edge by an interstitial cement, termed hyaluronic acid, which may be likened to the lignin and pectin in plant tissue. This thin layer of endothelial cells is continuous with the endothelial cells which line the arteries and veins. The capillaries are of varying sizes, ranging in diameter from 2 to 15 microns and in length from 0.25 to 0.75 mm. The smallest are found in the brain and the mucous membrane of the intestines, and the largest are those of the skin and the marrow of the bone.

A continous interchange of fluids occurs between the tissues and the blood stream. Some fluid leaves the blood at the arterial end of the capillary, carrying oxygen and nutrients to the cells of the body, and returns to the blood at the venous end of the capillary carrying away carbon dioxide and other waste products of metabolism. It is thus seen that the capillaries play a vital role in the proper functioning of the body as a whole.

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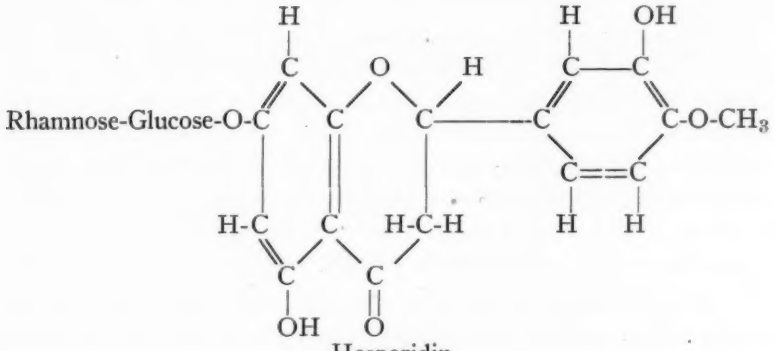
When the capillary walls become abnormally fragile, under certain conditions they are likely to break, thus allowing blood to permeate the surrounding tissue. This type of hemorrhage, which may be more or less extensive, depending on the number of capillaries concerned and the general state of the whole circulatory system, is due to the condition termed increased capillary fragility.

Chemistry and Properties

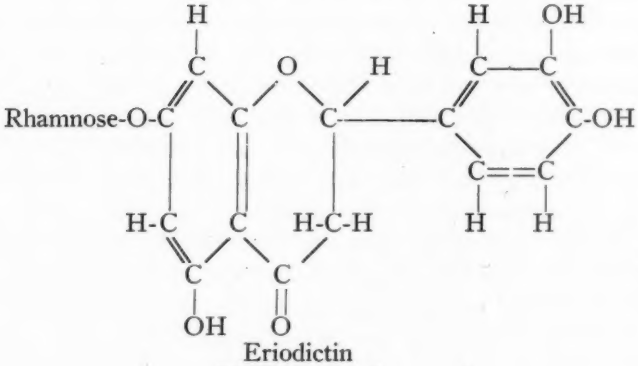
In 1936, Szent-Györgyi and co-workers (1) announced the discovery of a substance in citrus fruits and red peppers which would restore weakened capillaries to normal. This substance they named vitamin P because of its ability to reduce the permeability of capillaries. Upon further investigation they later reported that this substance was a glucoside, hesperidin (2), a recognized component of citrus fruits that had been known for over a century (3). As additional studies were carried out, it was soon found that the vitamin P activity of hesperidin resulted from some impurity in the original crude crystals. They later prepared a concentrate containing eriodictin, a compound chemically related to hesperidin. This substance was shown by clinical studies to be active in decreasing capillary fragility (4). In like manner the activity of this material was also found to be due to some impurity in the eriodictin concentrate. It was presently found that quercitrin, a related substance, was a component of these extracts. As a result of experiments on guinea pigs, it was concluded that this substance was inactive. From the experimental data these investigators concluded that vitamin C is needed to activate vitamin P and that when vitamin C is administered simultaneously, both hesperidin and eriodictin restore weakened capillaries to normal (4).

Meanwhile certain contradictory reports appeared (5, 6). Scarborough (7), Bachrach (8) and Bourne (9) published favorable results. Further search for this active constituent showed that many other fruits possibly contained this active factor. Higby (10) thought that the active component was a soluble form of hesperidin, the chalcone. Wawra and Webb (11) advanced a similar conclusion.

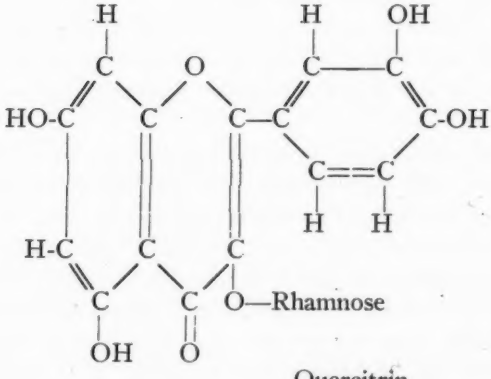
From the knowledge thus far of the chemistry of the active material, it was evident that the factor was probably of a flavonol structure. The chemical structures of the compounds are similar.



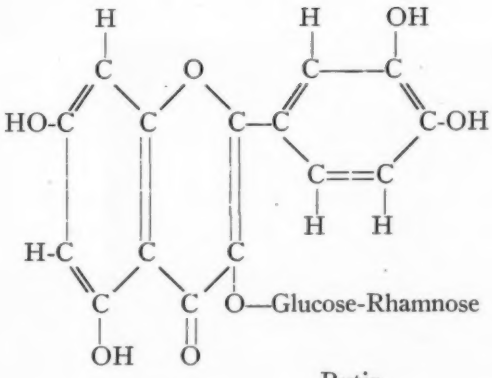
Hesperidin
(A Flavanone)



Eriodictin
(A Flavanone)



Quercitrin
(A Flavonol)



Rutin
(A Flavonol)

The flavonols contain an extra double bond and an extra hydroxyl group which gives to them greater physiological as well as chemical activity. Quercitrin, a flavonol, contains rhamnose as the sugar part of the molecule, whereas in rutin the sugar part of the molecule consists of glucose and rhamnose. James F. Couch of the Eastern Regional Research Laboratories, noting these similarities thought it possible that rutin may have a beneficial effect on abnormally fragile capillaries. Therapeutic use of rutin was started early in 1943 by Dr. John Q. Griffith, Jr., of the Robinette Foundation, Medical School, University of Pennsylvania; it was demonstrated that rutin is effective in reducing increased capillary fragility to normal (12). Clinical testing over a period of three years by many physicians has confirmed the value of rutin in certain cases of increased capillary fragility.

Rutin, $C_{27}H_{30}O_{16}.3H_2O$, may be prepared in a highly purified state. It is a yellow, tasteless, non-toxic powder consisting of masses of microscopic needle shaped crystals which become plastic at 182-192° C. and decompose sharply at 214-215° C. It is slightly soluble in cold water, approximately 0.13 Gm. per liter, and much more soluble in boiling water, from which it may be readily crystallized. It is more soluble in methanol, ethanol, acetone and ethyl acetate and very soluble in pyridine and alkaline solutions. It is insoluble in chloroform, ether, benzene and petroleum solvents. On exposure to light it gradually darkens and should be preserved in dark-colored bottles or in a dark place. On hydrolysis with dilute acids, rutin yields quercitrin, glucose and rhamnose.

FIGURE I

MICROPHOTOGRAPH OF RUTIN CRYSTALS

Sources

Rutin has been reported to be a constituent of a great number of species of plants among which may be mentioned buckwheat (*Fagopyrum esculentum*), tobacco (*Nicotiana tabacum*), forsythia (*Forsythia spendens* and *fortunei*), hydrangea (*Hydrangea paniculata*) and pansies (*Viola tricolor*). Rutin was reported in flue-cured tobacco by Hasegawa (13). Flue-cured tobacco of high quality was originally used to prepare rutin (14) at the Eastern Regional Research Laboratory, United States Department of Agriculture. The yield averaged about 0.4 per cent. Many other types of tobacco have been investigated, especially the air-cured varieties, which were found to contain only traces of rutin. Because of the low yield of rutin from an expensive raw material which manifested itself in a high cost of the drug, Couch, Naghaski and Krewson (15) began a search to find a more economical source of the drug. Of the many plants that they examined, buckwheat was found to be the most promising.

Rutin in buckwheat was first reported in the literature by Schunck (16) who found a yield of 0.11 per cent. Wunderlich (17) obtained "more than 2 per cent" from the dried blossoms of the plant. Brandl and Schärtle (18) reported 1.78 per cent from the fresh

leaves, 0.71 per cent from fresh flowers, 0.09 per cent from stems and 1.02 per cent from the dried whole plant. The research on buckwheat by Couch, Naghaski and Krewson (15) consisted of studies of the rutin content of buckwheat at different stages of growth and under various conditions of processing. They obtained a yield of from 3 to 5 per cent of rutin from buckwheat as compared to 0.4 per cent from tobacco, thus reducing the material cost of rutin from $135-$150 to approximately $1.10 per pound for the drug.

EASTERN REGIONAL RESEARCH LABORATORY
Chestnut Hill Station
Philadelphia, Pa.

The content of rutin is highest at the 3-5 blossom stage and decreases as the plant matures. Very little rutin is contained in the plant when it has gone to seed. A large percentage of rutin is lost when the plant is dried slowly, therefore rapid drying by a special process is essential if the dried plant is to be used in preparing the drug. Freshly harvested buckwheat may be used if facilities for immediate processing are at hand.

Preparation

The preparation of rutin from buckwheat may be made from either the fresh or the specially dried plant. To extract rutin from the fresh buckwheat (19), the uncut plant is macerated in alcohol for 24 hours, the solution drawn off, replaced by fresh alcohol and again macerated for 24 hours. Ninety-five to ninety-seven per cent of the rutin will have been extracted from the plant. Upon concentration of the alcoholic extract by distillation, a mixture of rutin, fats and other plant constituents is obtained. When this is cooled, rutin crystals form. The mixture is filtered, the rutin dried and extracted with benzene to remove the fats. The crude rutin is then recrystallized twice from water to obtain a pure product.

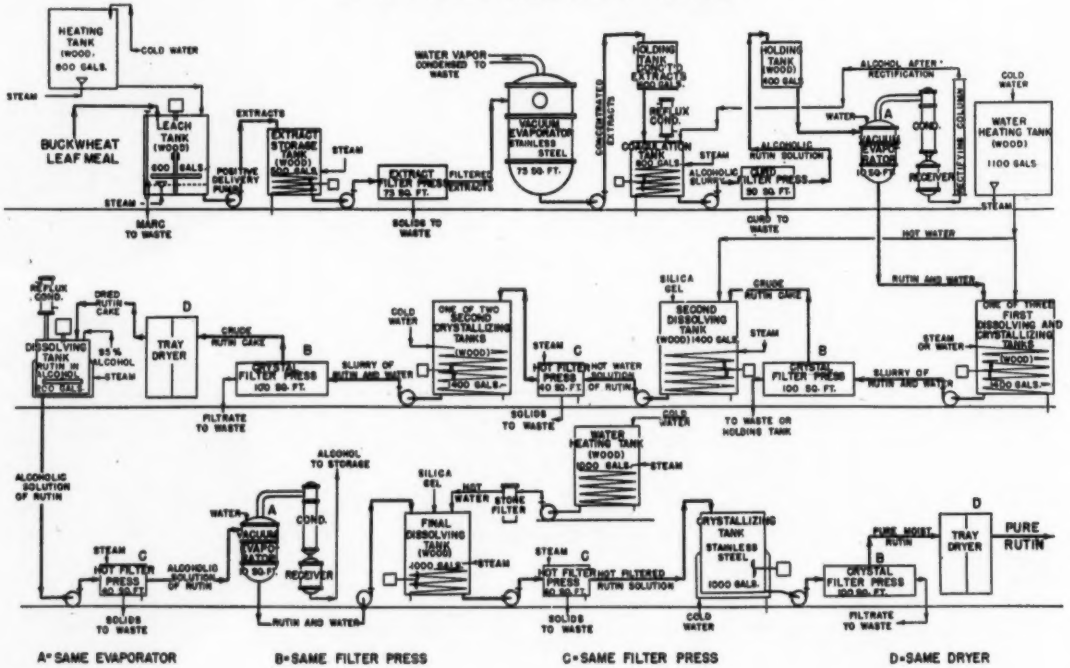
Two methods for the extraction of rutin from dried buckwheat leaf meal have been developed in the pilot-plant at the Eastern Regional Research Laboratories in the Chemical Engineering and Development Division (20). One method utilizes hot water as the solvent. The leaf and flower material is separated from the stem and ground to form a coarse meal. Three 30 minute extractions are made, which removes 97 per cent of the rutin. The extract is filtered, concentrated by vacuum evaporation, protein and colloidal material coagulated with 95 per cent alcohol and removed by filtration. The filtrate is evaporated until nearly all of the alcohol is removed, resulting in the crystallization of the crude rutin. This crude rutin is purified by further recrystallization. In the second method, 70 per cent alcohol is the solvent. The leaf meal, prepared as previously described, is treated with three 12 hour extractions. The extracts are concentrated by vacuum evaporation. Fats and other plant constituents are also extracted by dilute alcohol, and must be removed. These are eliminated by hot filtration and benzene extraction. The filtrates are then purified in a manner similar to that used in the hot water extraction method.

Clinical Studies

The medical uses of rutin are based on its property to reduce increased capillary fragility to normal. In various disease conditions in which hemorrhage or weakened capillaries occur, extensive clinical studies have demonstrated the value of rutin.

FIGURE II

FLOW DIAGRAM FOR PRODUCTION OF RUTIN FROM BUCKWHEAT LEAF MEAL BY HOT WATER EXTRACTION PROCESS



No toxic effects have been observed with rutin and it is devoid of cumulative action. Rutin has been tested on laboratory animals by the Pharmacology Laboratory of the Bureau of Agriculture and Industrial Chemistry and also by the Bureau of Animal Industry. No definite evidence of acute or chronic toxicity was found. Dr. J. Q. Griffith, Jr., of the University of Pennsylvania, was the first to carry out clinical investigations. He has found no indications of toxic effect from the drug in a large number of patients he has been treating daily for periods up to 30 months. Approximately 200 physicians, hospital clinics and research workers have been supplied with rutin for medical study. Clinical results of their findings were presented by James F. Couch and Dr. J. Q. Griffith, Jr., before the Division of Medicinal Chemistry of the American Chemical Society at the Atlantic City meeting, April 12, 1946. A summary follows:

Since 1943 over one thousand cases have been studied. The Gothlin technique (21) for measuring capillary fragility indicated that 255 or 21 per cent of these cases had an increased capillary fragility. Rutin was administered to these patients in doses of from 60 to 120 mg. per day. Only a small number of these patients required more than 60 mg. per day. In one patient, who was allergic to buckwheat, the rutin was discontinued and crude hesperidin substituted. No toxic effect was observed in any of these patients. The following data refers to 173 cases in which there was adequate follow-up. A number of these cases have been under observation for as long as 2½ years.

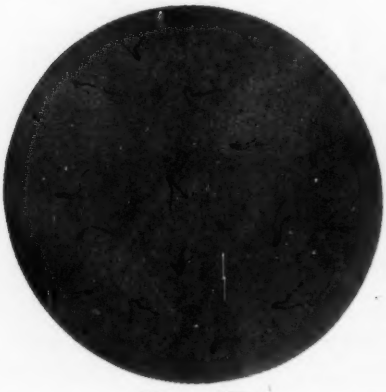


FIGURE III
NORMAL CAPILLARIES AND VESSELS OF THE SUBPAPILLARY PLEXUS

FIGURE IV
SOMEWHAT DILATED NORMAL CAPILLARIES WITH HEMORRHAGE SPOT

Normal capillary fragility was observed in 152 cases (88%). In 21 (12%) increased capillary fragility remained or returned after having been normal. Of these, 15 had been under observation for 6 months or less.

Of the adequately studied cases, 20 (11.5%), had a history of apoplexy. Capillary fragility became normal in all of these cases, and there have been no further attacks.

Retinal hemorrhage, a type of hemorrhage which causes partial or even complete blindness, had occurred in 20 (11.5%) cases. Normal capillary fragility was restored in 17 (85%) of these cases. Increased capillary fragility remained in 3 of these cases, in which the treatment with rutin was four months or less. In 5 patients further retinal hemorrhage occurred.

While rutin is not recommended for the treatment of hypertension, there was a lowering of blood pressure in 63 (36%) cases. Moderate lowering was observed in 52 cases and in 11 cases there was a marked lowering.

Potassium thiocyanate, when used in the treatment of hypertension, has the property of weakening the capillaries of some patients. The drug, therefore, must be used with great caution. If the patient is given rutin, the tendency for the capillaries to weaken does not occur. Similar effects have been observed in the use of salicylates and arsenicals, and rutin may be combined with these drugs to keep the capillary resistance at a normal level.

Rutin has been found a valuable drug in diabetic retinitis, a condition in diabetics in which there are retinal hemorrhages.

Two cases of pulmonary hemorrhage of undetermined cause and not due to tuberculosis have been arrested by treatment with rutin (22). The hemorrhage had occurred for a long period of time, and all measures to control it had failed. After administration of rutin for from 2 to 3 weeks, the hemorrhage ceased and there has been no recurrence.

Rutin should be continued, even after these conditions have been brought to normal, as the affection may return if the rutin is discontinued. Reports have indicated that relapses have followed discontinuance of the drug. Upon resumption of rutin therapy normal conditions were again restored. It has also been reported that rutin is much less effective if there exists a simultaneous vitamin C

deficiency. It is therefore important that the patient have an adequate intake of this vitamin.

Recent research indicates the possibility that rutin may have nutritional value. Further investigation of the use of the drug in this respect is expected. The studies at this time point to the opinion that rutin could serve the circulatory system in a manner similar to that of vitamin C in the growth and hardness of teeth and bone.

It has been estimated that approximately 1,300,000 pounds of rutin will be required annually for the medicinal and for the possible nutritional requirements of the United States. For 1946 the estimate has been placed at 10,000 pounds. As a result of the small scale experimental manufacture of the drug in cooperation with the staff at the Eastern Regional Research Laboratory, a number of pharmaceutical houses are planning commercial production of the drug in 1946.

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ORGANIZING A MULE

By T. Swann Harding

A MULE is a very slightly organized affair. The psychology of mules is such as to rebel at organization. Occasionally scientific research during peacetime appears to partake of the psychology of the mule. For, no sooner did the war end than prominent research directors began to tell us that scientific investigation could no longer be "regimented" as in wartime. Yet that wartime regimentation represented little more than the rational organization research should undergo at all times, and *it produced results.*

Take the development of the proximity fuse. It was an amazing thing. Scientists were asked to produce a shell containing a delicate brain which would tip it off just when to explode. That brain must send out signals which would rebound from solid objects, and thus tip off the brain to explode the shell. Shells were finally produced so delicate in mechanism that they would turn their fuses towards a man who entered a large room containing piles of them. Yet that delicate mechanism could survive being fired from a gun!

How was that done? By sound organization and competent leadership. The problem was segmented into fragments. Teams of scientists with the requisite specialized training were set to solve portions of the problems. If one part-problem seemed extremely difficult two or three teams would be set on it. Sometimes only one team came through with a solution; sometimes three solutions turned up and the best could be selected. All told, the over-all problem was licked in a mere fraction of time it would have taken uncoordinated, disorganized science to lick it at peace.

Well, then, shouldn't research be organized at peace? If so, how much?

A very considerable controversy was precipitated about this question with the fall of the first atomic bomb and subsidiary revelations regarding its invention and manufacture. It seems perfectly clear that success with the bomb, as with the proximity fuse, and with dichloro-diphenyl-trichloro-ethane (DDT) proved the value and the supreme importance of governmentally coordinated and highly or-

ganized research. The President said as much in his Message to Congress of September 6, 1945.

But when Dr. Vannevar Bush, of the Office of Scientific Research and Development, hinted politely that a little coordination would not go amiss in research at peace, there were impolite hisses and Bronx cheers from unexpected quarters. What happened in the case of the bomb is now well known. But there were very similar developments, though on smaller scale, in the insecticide field.

DDT was first synthesized in 1874. That was done by a German organic chemist who apparently had no suspicion of its insecticidal properties. He was a plodding research worker who accepted the tedious routine of preparing different organic chemicals. It was not until 1939 that the firm of J. R. Geigy, of Switzerland, reported that the compound was an effective insecticide against clothes moths and certain agricultural insect pests, and procured patents on its use for such purposes.

When the United States got into the war the possibility of louse-spread typhus agitated the armed services and they wanted something to kill lice without delay. So funds in the neighborhood of $400,000 were allotted by the Office of Scientific Research and Development and the National Research Council to expand a small entomological laboratory the Department of Agriculture had at Orlando, Fla. Ultimately about seventy-five employees were housed there in several frame buildings and intensive work began.

The scientists in various specialties were organized into teams under project leaders. The hours were long, the work was hard, and the regimentation might have been called severe, except that everybody was stimulated and happy and things went smoothly and efficiently. Tests were made on as many as a thousand substances monthly, sent in as possibly having insecticidal value. DDT proved the best of all of these, and its story is well known to everyone. Its rapid development and application we owe to highly organized research.

But work went on as well upon mosquito repellants, substances to destroy mosquito larvae and adults, and effective methods of controlling the mites which cause chiggers. Many important facts were found out which prove useful in campaigns to destroy houseflies, blowflies, bedbugs, cockroaches, fleas and scabies mites. Some important leads could not be followed at the time because the urgency

of the work was so great, but all were outlined for future investigation. Again organization did the job and did it quickly and well.

It was proved in many fields of wartime research that sound organization, competent leadership, intensive application, efficient methods and adequate funds could accelerate the progress of science tremendously. For instance a quarter century's progress on the atomic bomb was compressed into two years, and there was a similar saving of time in the field of insecticides. In the case of the atomic bomb a sum of two billion dollars was freely appropriated, two entire large cities were constructed, 125,000 workers were utilized, and a top team of international scientists directed the whole.

Take cancer for comparison. The cancer problem (like that of the common cold and of rheumatism) is still with us. That it could be solved rather quickly by properly financed and organized research, carried on intensively by teams of specialists, appears to have been proved by what was accomplished in wartime research. Moreover it brings a death quite as horrible as any war produces to as many people per year as we lost in two years of the world war just ended.

In 1937, when Congress actually granted, not two billions, but a mere $750,000 to finance a National Cancer Institute, and $700,000 a year to operate it, we thought that exceedingly exciting news. Until the Alfred P. Sloane Foundation grant, in August, 1945, of four million dollars for the study of cancer, endowments for this purpose amounted to only about five millions in this country, and the total grants of all American foundations for all research in medicine and health was only five million dollars in the last peacetime year, 1940. Yet we spare fifteen millions a year for infantile paralysis, a much less common or menacing disease!

What is worse, cancer research, like much medical and biological research generally, has been carried on by slap-dash, haphazard, laissez-faire methods, in an old tradition unfit for a modern scientific age. This has coupled first-class brains with slovenly work habits, considerable secrecy, too much playing for prestige, some outright quackery, and large wastage of funds. What a leader in this field, the late Dr. James Ewing, had to say in 1938, still holds much too largely.

To start with, much money is wasted in cancer research by well-meaning philanthropists who misunderstand the nature of the problem the disease presents, who hope to find an immediate cure, and

who get taken in by quacks. These quacks use research as a racket. But the useful research in this difficult field must be basic in character, and it is extremely unlikely to yield any practical, beneficial results immediately. Yet persons of large means have often made the mistake of granting money for the direct discovery of the cause and cure of cancer.

Some make the mistake of listening to "fervid tales of pseudoscientific adventurers or outright imposters, who begin by decrying the methods of orthodox medicine. . . . The benefactor knows nothing about medicine and the pseudoscientist nothing about cancer, and both cordially deceive the other." Many projects of this sort have grown to enormous proportions, involving the expenditure of millions, deceiving thousands of patients, surviving repeated public exposures, and then migrating to new territory, yet often gaining steadily in support.

Often the wealthy and socially elect laymen supply funds to support a "persecuted" scientist who is a veritable charlatan. Such pseudo-scientists frequently get into very respectable laboratories because they have big backing. Benefactors usually have high intelligence and deficient sagacity. The life of such projects to find cancer cures is unfortunately long. Lack of system and disorganization attract inferior, incompetent, notoriety seekers to the field.

Foundations often grant funds to investigators having no broad plan and limited experience. Professors who present projects may secure funds, and undertake work which stops abruptly if they leave the institution or are promoted to administrative jobs. Mapping of the entire field, to find and fill the gaps, and sound organization are conspicuously lacking. Biological research by supercilious prima donnas is always bad and far too common. Cancer investigation is much too compartmentalized and few specialists see beyond their own science, their own methods, their own attack on the problem.

Fundamental is the fact that cancer is not a simple disease. It is a basic growth abnormality which ramifies in many ways and produces a complex of diseases. It is therefore unscientific to seek the cause and cure of cancer. The causes of malignant growth embrace all classes of forces known in nature, and the malignant growth process is still as obscure as that of normal growth which we understand only slightly. Various approaches suggest themselves, among them the statistical and the genetic.

Chemical studies should be made of normal and abnormal growth and tissue metabolism. Substances should be searched out which will scotch the cancer and not injure the sufferer. Physical chemistry, theories of osmosis, embryonic organizers and inducers, parasites, ultrafiltrable viruses, chemicals which cause cancer or which control the growth of processes of organisms, X-rays, clinical and pathological investigations as to the relationship between injuries and the occurrence of cancer—all these and many more angles must be considered.

Hence organized teamwork under an over-all board of strategy is the basic necessity. The entire field could be mapped and gaps filled in by cooperative effort. There would be constant interchange of information between laboratories and workers. Each specialist could still carry on in his own laboratory, but his work would be correlated with that of others through a national institution, say the National Cancer Institute itself, acting as a clearing house and guide. Specialists would be organized in teams created to work intensively on specific aspects of the problem.

While one would be radical indeed to suggest that the solution of the peacetime cancer problem was as important as devising means of vaporizing cities and their inhabitants, it does seem that it would not be too impudent to suggest research funds for a quarter of a billion dollars to finance this drive. That would be an eighth what it cost to find efficient means of mass murder and property destruction, and this seems within reason.

In addition to adequate funds, scientific organization of research is paramount. Industrial research is quite well organized for its purposes. Agricultural research is carried on in a fairly well coordinated Federal-State network of laboratories and institutions, with the Office of Experiment Stations in the Department of Agriculture acting as general strategy board and clearing house for seven or eight thousand projects carried on jointly. The Department's own research is also well organized.

However much academic and institutional investigation, particularly in biological science, has long been carried on by the laissez-faire, prima donna method. It has been too much compartmentalized. Few things are as unscientifically organized and planned as is most fundamental research. Above all there is most urgently needed a national over-all coordinating agency, an Institute of Science, to aid

in mapping entire fields and completing the maps through well-correlated effort.

Those who object to the organization of research often say that it can no more be organized than can painting or writing or the arts generally. Yet even those who write and paint accomplish far more by systematic, well-planned effort, than if they work hit-or-miss. Much of their work also is a dull routine and this certainly can be well organized. A great deal of scientific research also is of purely routine character.

Some brilliant worker somewhere makes an outstanding discovery, develops a new method, observes something hitherto neglected. At once a hundred run-of-the-mine workers in a score of laboratories can follow the fashion, confirming, confuting, and so on. If a new element or compound is produced, then thousands of tests must be made of its physical constants. There also remain thousands of organic chemicals to be synthesized, many of which, like DDT, may turn out much later to be quite valuable.

When certain investigators found out that the addition of milk to a supposedly complete rat diet produced unexpected results, things began to happen all over the place. The enormous structure of research on the place of vitamins and minerals in the diet and in therapy was erected upon this observation. Again, when one investigator found out that thyroid substance affected the size and composition of rat bones, there was room for a couple of hundred papers by others on the effects of any ductless gland upon any bone, with due allowance for sex, nutrition, age, and exercise level of the animal.

All this work should be done, but it can be planned on a mass-production basis. There is nothing to differentiate it from a series of analysis of milk, fertilizer or fishcakes. Competent direction could make it highly efficient in operation. Yet in dozens of laboratories it also is carried on with all the meticulous slowness and sanctity that the noblest of pure research is supposed to, but does not, require. Workers look aloft as if for inspiration and await the afflatus. They are also wasteful, extravagant and often indolent and incompetent.

No one genius produces atomic bombs, DDT, penicillin or radar. It takes highly organized and competently led and supervised teams of specialists. But a quarter of century of progress in atomic physics and chemistry can be compressed into two short years when the

information is needed for purposes of destruction. Yet you can wager it will take far longer than that to release atomic energy for constructive peacetime purposes, mainly because organization will be lacking.

Yet we know that with adequate funds, competent leadership and scientific organization science can solve practically any problem now confronting the human race. Human beings have proved it can be done in emergencies. They must now defy tradition and achieve the same sort of accomplishments at peace. Cancer is on the way out as a human scourge as soon as science organizes to conquer it. The psychology of the mule should not prevent such organization.

SELECTED ABSTRACTS

Studies on the Toxicity of Streptomycin for Man: A Preliminary Report. R. A. Hettig and J. D. Adcock. *Science 103,* 355 (1946). Streptomycin was administered to nine patients in total dosages varying from 1,850,000 units given over a period of forty-eight hours to 72,250,000 units given over a period of fifty-six days. Six of the patients received the drug by intermittent intramuscular injections at intervals of three to four hours, two cases received it by continuous intravenous infusion, and one by continuous hypodermoclysis. One patient also received 40,000,000 units of the antibiotic orally over a period of eleven days, in addition to parenteral administration.

Tests of renal and hepatic function, as well as blood studies, were carried out immediately prior to the start of therapy and within ninety-six hours after its termination. Urinalyses were also performed frequently before, during, and following the course of treatment.

No impairment of hepatic or renal function was noted during the investigation. In one case a microscopic hematuria developed, and in another a slight albuminuria and the presence of hyaline and finely granular casts were observed. Both of these abnormalities were transient. No significant decrease of the hemoglobin or erythrocyte levels occurred. In one case there was a decrease in the leucocyte count at the end of a forty-five day trial, but this condition persisted for only a few days.

Minor drug reactions noted were believed attributable to impurities present in the streptomycin used, particularly that available early in the series. One type of reaction resembled the rsponse to histamine, with facial flushing, headache and fall of blood pressure lasting from ten to sixty minutes. A second type of reaction appeared in from one to several days after treatment had been started; this included fever accompanied by myalgias and arthralgias. Skin eruptions were noted in two cases.

Auditory Impairment Caused by Drugs. J. C. Howard, Jr. *U. S. Naval Med. Bull. 46,* 387 (1946). The observation of 1,000 consecutive patients with bilateral deafness seen at a naval hospital revealed that only 14 cases were caused by the administration of drugs; of these, quinine was responsible for twelve of the cases, and salicylates for two.

The criterion for a diagnosis of deafness was the loss of at least 30 decibels in the better ear between the frequencies of 256 to 2,048, generally considered to be the conversational range.

The administration of rather massive doses of atabrine was found to have little or no effect on the hearing of 126 men tested.

Quinidine is stated to be slightly more toxic to the aural mechanism than quinine. The author discusses briefly the physiological changes resulting in deafness which are brought about by quinine, salicylates, arsenic, phosphorus and oil of chenopodium.

Caution in therapy, particularly in the administration of quinine and salicylates, is advised in patients with a history either of previous aural disease or of exposure to heavy gunfire, especially when tinnitus is present.

Acute Atabrine Intoxication: Report of a Case. R. C. Burnham. *U. S. Naval Med. Bull. 46,* 434 (1946). The author reviews the reports of studies on the toxicity of atabrine to experimental animals and in clinical use in man. He presents in considerable detail a case report of a patient who ingested a quantity of atabrine tablets, believed to represent about 90 grains of the drug, in an unsuccessful attempt to commit suicide.

The patient first experienced dizziness and blurring of vision; vomiting and convulsions followed. The pulse was 90, thready and weak; blood pressure was 78/60.

Treatment consisted of gastric lavage, followed by the intravenous administration of 5 per cent dextrose in saline solution, eight liters of which were given over a period of about forty-eight hours. Oxygen was administered by nasal catheter during this time. After the oxygen and infusion therapy had been discontinued, one ounce of brewer's yeast per day was given.

Recovery was complete and rapid. No evidence of liver damage was found. The leukocyte count was 8,850 on the twelfth day, whereas it had been 16,300 by the end of the first day. A yellow coloration of the skin was still evident after one month. A blood level determination of the drug, performed on the second day, revealed the presence of 475 gammas, 25 gammas below the maximum carrying capacity of the blood.

The psychiatric aspects of the case are discussed as representative of the motivation for certain suicides.

A Buffered Basis for Penicillin Cream. W. N. Hailstone. *Pharm. J. 102,* 177 (1946). It has been stated by the manufacturers of Lanette wax SX that if this product is heated above 115° it tends to hydrolyze, with the production of an acid reaction. In order to produce a final pH of 7.5 it has been recommended that a mixture of 2 parts of boric acid and 1 part of borax should be added in the proportion of 1 per cent of the Lanette wax SX used. It was found, however, that the addition of 5 per cent of glycerin to a 25 per cent Lanette wax SX cream, buffered with this mixture, reduced the pH to about 6.2 because of the increased ionization of the boric acid.

Studies were made on a buffer solution containing 10 per cent of sodium phosphate, 1 per cent of sodium acid phosphate and 1 per cent of phenoxetol. The addition of glycerin to this buffer produced no noticeable change in pH. It was found that if 5 mils of buffer solution are present in not more than 35 gm. of a 30 per cent Lanette wax SX cream, the final pH will be 7.35 ± 0.05; for not more than 57 gm. of cream, 7.3 ± 0.1. Five mils of buffer solution are sufficient for 70 gm. of a cream containing 15 per of Lanette wax SX and 15 per cent of peanut oil.

The pH of a sample of cream containing the phosphate buffer was found to remain constant at 7.4 after autoclaving at 15 lb. for one hour, whereas the pH of a control sample containing no buffer was altered from an initial value of 6.8-7.2 to 6.0, and that of a sample containing the boric acid buffer changed from 8.0 to a final value of over 7.6.

It was observed that the cream buffered with phosphate suffered some loss of viscosity on autoclaving, but the author reports that this may be overcome by first autoclaving 5 mil quantities of the buffer solution, dissolving the penicillin in it, and adding this to the unadjusted base.

The Copper Ionization Treatment of Fungous Infections. W. J. Lahey and J. E. Byrnes. *U. S. Naval Med. Bull. 46,* 554 (1946). The copper ionization bath treatment of fungous infections of either the interdigital or dyshydrotic (thick-walled blister) types was found to be a safe and valuable mode of therapy in 154 cases.

The baths were constructed and operated according to the method described by Knox, with several minor alterations. Two indifferent electrodes were used in order to permit the simultaneous treatment of both feet. The four 1½-volt dry cells were replaced after 120 treatments, and the 0.2 per cent copper sulfate solution was changed weekly.

A test treatment of two minutes was first given in order to determine the sensitivity of the patient to copper. Subsequent treatments were of six minutes' duration, on alternate days. The affected parts were thereafter dried, and dry, sterile dressings were applied to any lesions. No powders were applied between baths.

Complete healing occurred in 65 per cent of the cases and improvement in 23 per cent, although persistent scaling or fissuring were noted in the latter group after the disappearance of acute signs. In subsequent cases the use of keratolytic agents was found to complete the healing process.

No reactions attributable to copper sensitivity were observed. Several patients developed a transient follicular rash at the points of application of the electrodes.

SOLID EXTRACTS

A new insect killer ten times more potent than DDT is now under field test. Known as 666 and chemically the gamma isomer of hexachlorocylcohexane, this substance was developed in Britain as a war research project.

The most promising application for 666 is in the destruction of cotton insects such as the boll weevil, cotton aphids, cotton fleahopper, etc., which take an annual tool of $140,000,000 in U. S. crops.

Combinations of 666 with DDT are considered to be superior to either alone since although 666 has more rapid action it is not as permanent, surfaces losing their killing effect in a few days.

AJP

A long term study with BCG vaccine among American Indians has given results which indicate that it has marked protective action in preventing tuberculosis. Mortality and morbidity figures are quite definite in pointing to its value when properly used. The choice of American Indians as test subjects was based on their known high susceptibility to tuberculosis. The use of this vaccine for those whose work subjects them to continued exposure is suggested.

AJP

According to available statistics a patient was admitted to a hospital every 1.9 seconds in the United States during 1945. It is quite clear to a competent observer that hospital service will be in greater and greater demand in future years. The public is convinced that home is not the place for the sick and the growth of hospitalization insurance plans has given more people the financial means to obtain the service when needed.

AJP

Atomic energy has at last invaded the drug field! Radioactive iodine has been reported as an effective means of treating toxic goitre. The product is taken orally and when dissolved in water in the small

amount used does not even impart to it a taste. Its effectiveness is due to the fact that iodine is trapped by the thyroid gland and in this case it bombards the tissue with the products of its disintegration destroying a large part of the cells producing thyroxin. The treatment appears to be quite favorable when compared with surgery or thiouracil.

AJP

The observation that penicillin therapy of primary syphilis since May, 1944, has not been as satisfactory as in earlier cases has been explained by the fact that penicillin K has been present in commercial penicillins in greater amounts. Penicillin K is inactivated by body fluids and thus *in vitro* methods for evaluating penicillin do not give true results. Penicillin producers are now taking steps to reduce the penicillin K content of their product.

AJP

The tropical or exotic diseases differ chiefly from those of temperate climates in that they are usually spread by some vector and control methods must necessarily center around the elimination of the vector. Thus the louse transmits typhus and relapsing fever, the fly trachoma, the mosquito malaria and the snail schistosomiasis. Some peculiar observations have been made. For example, the snails in streams flowing toward the east coast of South Africa are infested with the parasites, whereas streams having a common origin in the highlands, near Johannesburg, but flowing toward the west coast rarely contain infected snails. To know the answer to this anomaly might provide a clue in the control of this serious tropical disease.

AJP

The mechanism of rheumatic fever is still not clearly understood and yet it affects over one million persons in the United States. It seems likely that the damage done is due to some interference in an important enzyme system. It is known that salicylates alleviate the disease manifestations and the sulfonamides aggravate the condition.

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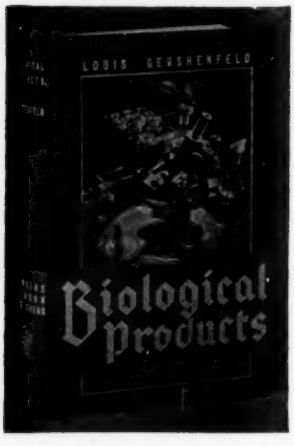

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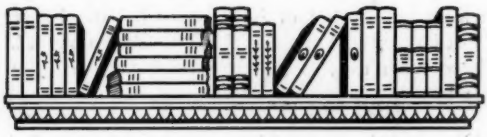

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